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Tissue-engineering strategies, prosthodontic potential and clinical-translation challenges of regenerative teeth

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Abstract. Although traditional oral prosthetic approaches such as dental implants and fixed bridges have been widely applied, they are limited by the absence of proprioception and periodontal ligament–mediated buffering. With advances in regenerative medicine, particularly stem-cell technology and tissue engineering, replacing artificial teeth with "bio-teeth" has become a research hotspot in the field of oral rehabilitation. Based on the three core elements of tissue engineering—seed cells, scaffold materials and growth factors—this review summarizes research progress in three major technical routes: pulp-dentin complex regeneration, bio-root regeneration and whole-tooth regeneration, and analyzes the application potential and existing limitations of each route. On this basis, the core challenges facing the clinical translation of regenerative-tooth technology are discussed, including the bottleneck of vascularization, difficulties in morphological control and the complexity of the oral immune microenvironment. A comparative analysis with current mainstream prosthetic schemes is also conducted to explore potential combined-application strategies in the future. In the short term, regenerative teeth cannot completely replace conventional prosthetic treatments and may instead complement existing approaches such as implant restoration and fixed bridges. Current animal studies and limited early-stage clinical trials indicate that regenerative-tooth technology is expected to drive the transformation of oral rehabilitation from the "artificial substitution" mode to "biological reconstruction". Nevertheless, its mature clinical application still requires sustained interdisciplinary collaborative research.

Keywords: regenerative tooth, pulp regeneration, tissue engineering, oral rehabilitation, bio-root

1. Introduction

In current clinical practice, dental implants have been widely regarded as one of the mainstream treatment options for missing-tooth rehabilitation, with favorable 5- to 10-year survival rates. A large-sample cohort study including 10,871 implants with a maximum follow-up of 22 years reported that the 5-year cumulative survival rate of dental implants reached 98.5 %, and the 10-year cumulative survival rate was approximately 96.8% [1]. Multiple systematic reviews have drawn similar conclusions: the implant-level 10-year survival rate is around 96.4 % (95 % CI: 95.2 %-97.5 %), and long-term (10-25 years) survival rates range from 90 % to 98 % [2, 3]. Nevertheless, this restorative approach has notable limitations. Implants lack the periodontal ligament structure and proprioception of natural teeth. Force buffering during mastication mainly relies on the osseointegrated interface rather than the elastic suspension mechanism provided by the periodontal ligament.

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Furthermore, the relatively high treatment cost places a substantial financial burden on many patients. These drawbacks have prompted researchers to consider whether a biologically functional tooth can be fundamentally reconstructed. The rise of regenerative medicine has offered a new perspective on this issue. Over the past one or two decades, substantial advances in stem-cell biology, tissue-engineering materials science, and developmental biology have rendered tooth regeneration via tissue-engineering strategies no longer an unrealistic vision [4]. Regenerative teeth refer to reconstructed complexes containing pulp, dentin, periodontal ligament and even a complete anatomical crown, which are fabricated at the defect site using cells and scaffold materials. They are designed to mimic the functional and anatomical features of natural teeth, rather than serve as artificial substitutes made of metal or ceramic, as in conventional dental implants [5].

This paper presents a narrative review of the major technical routes in regenerative-tooth research, with an emphasis on the core problems solved and the remaining shortcomings of each strategy. Following the fundamental framework of tissue engineering—seed cells, scaffold materials and local microenvironment—this review first summarizes research progress in pulp-dentin complex regeneration, then discusses the construction of bio-roots and whole teeth, and finally analyzes practical barriers hindering the clinical translation of these technologies. This review focuses primarily on tissue-engineering-mediated regenerative strategies and does not cover whole-tooth induction techniques that modulate endogenous developmental signals using antibodies or other pharmacological agents.

2. Core tissue-engineering elements for regenerative-tooth construction

2.1. Sources and characteristics of seed cells and strategies for pulp regeneration

The selection of seed cells constitutes the primary step for regenerative-tooth construction. Dental Pulp Stem Cells (DPSCs) are the most commonly used cell type in pulp-regeneration experiments. Derived from the neural crest, these cells possess satisfactory in-vitro expansion capacity and multilineage differentiation potential [6]. DPSCs feature convenient access to tissue sources and prominent capabilities of cell proliferation and odontogenic differentiation. Nevertheless, their cell sources are limited, as they can only be harvested from healthily extracted teeth, yielding a restricted cell quantity. Animal studies have confirmed that the implantation of DPSCs combined with appropriate carrier materials in-vivo can promote the formation of pulp-like tissue, with potential to support vascularization and neurogenesis [7].

Apart from dental pulp stem cells, induced Pluripotent Stem Cells (iPSCs) have attracted increasing attention in recent years. iPSCs can be obtained by reprogramming somatic cells (e.g. skin fibroblasts). Theoretically, they can circumvent ethical controversies associated with embryonic stem cells and provide autologous seed-cell sources. Several research teams have attempted to directionally induce human-derived iPSCs into dental epithelium-like cells, however, their directed-differentiation efficiency, cellular safety and standardized preparation protocols still require further validation [4].

Two major therapeutic strategies are currently available in the field of pulp regeneration. The first is the cell-transplantation strategy, in which stem cells expanded and cultured in-vitro are combined with scaffold materials and directly implanted into the root-canal system. Cells within the graft then form new pulp tissue in-situ. The second strategy is the cell-homing strategy. Instead of implanting exogenous cells, specific signaling molecules (such as chemokines) are delivered into the root canal to induce endogenous stem cells from the patient's periapical tissues to migrate into the root canal and initiate the repair process [8]. Each strategy has specific indications. The cell-transplantation strategy allows better control over cell quantity and quality, yet it requires long-term in-vitro culture at high costs, and carries a risk of immune rejection when allogeneic cells are adopted. The cell-homing strategy offers advantages in operational simplicity and

avoidance of immune-rejection risks. However, its therapeutic efficacy is highly dependent on the biological status of the patient's own stem cells. Homing efficiency may be markedly impaired in elderly patients or those with chronic periapical inflammation [8, 9]. Consequently, neither strategy can replace the other at present, and treatment selection should be determined according to specific clinical scenarios.

2.2. Scaffold materials and regulatory effects of growth factors

Scaffold materials provide three-dimensional support for seed cells to adhere, proliferate, and differentiate. An ideal scaffold should possess interconnected porous structures and favorable biocompatibility, and its degradation rate should be roughly matched with the rate of new tissue formation [5].

Degradable polymer scaffolds are a commonly used type of scaffold in tooth regeneration and can be broadly classified into natural and synthetic polymer scaffolds. Natural polymer scaffolds (e.g., collagen, chitosan) exhibit excellent biocompatibility and cell adhesion, however, they are characterized by relatively weak mechanical properties and difficulty in precisely regulating the degradation rate. Synthetic polymer scaffolds (e.g., PLA, PLGA) possess controllable mechanical properties and tunable degradation periods, yet their cell affinity is relatively poor, and surface modification is generally required. In experiments on biological tooth root construction, Stem Cells from the Apical Papilla (SCAP) and Periodontal Ligament Stem Cells (PDLSCs) have been co-seeded onto degradable polymer scaffolds and implanted into animal jawbones, whereupon the formation of tooth root-like structures was observed [10].

Growth factors play an irreplaceable role in regulating the direction of cell differentiation. The roles of developmental signaling pathways, including BMP, FGF, Wnt, and SHH, in early tooth development have been well validated. These pathways are involved in the regulation of key processes such as cusp morphogenesis and root elongation [9]. Among them, BMP primarily regulates the secretion and mineralization of the dentin matrix, the Wnt pathway participates in root development and periodontal ligament cell differentiation, FGF mediates cell proliferation and migration, modulating the mesenchymal-epithelial interactions of the tooth germ, and SHH governs the initiation of tooth germ development and cusp morphogenesis.

However, the signals during natural tooth germ development exhibit dynamic changes, with different types and concentrations of signals required at different time points and spatial locations. Most in vitro experiments currently cannot reproduce such precise spatiotemporal control over signal delivery. Resolving this issue relies on further breakthroughs in materials science and drug delivery technologies.

3. Major regenerative pathways and their clinical application prospects

3.1. Clinical value of pulp regeneration with revascularization and reinnervation

The dental pulp of natural teeth is not merely a connective tissue filler. It contains blood vessels that provide nutrition, nerve fibers that conduct sensation, and immune cells that participate in local defense. Although conventional root canal therapy can eliminate the infected pulp and complete root canal filling, the remaining tooth tissue and its fracture resistance may be compromised as a result of caries, access cavity preparation, and subsequent restorative procedures. In contrast, the goal of pulp regeneration is to reconstruct vital pulp tissue with vascular and neural networks after debridement [11]. To date, pulp regeneration has been explored in a number of animal experiments and early-stage clinical investigations. Vascularized and reinnervated pulp-like tissue has been successfully generated within root canals in animal models, however, a substantial gap remains between these experimental findings and widespread clinical application, and the lack of robust long-term clinical evidence continues to hinder clinical translation.

3.2. Biological tooth root regeneration

For cases of complete tooth loss, pulp regeneration alone is no longer sufficient to solve the problem, and attention must be directed toward the construction of biological tooth roots and even whole teeth. The concept of a biological tooth root is relatively straightforward: rather than replicating an entire tooth, the aim is to reconstruct a root-like structure with an associated periodontal ligament within the alveolar bone, which can subsequently support a dental crown. The presence of the periodontal ligament enables the regenerated root to provide physiological cushioning similar to that of a natural tooth, which, from a biomechanical perspective, offers advantages over the rigid osseointegration of dental implants [10]. Animal experimental studies have confirmed that stem cell–scaffold complexes can form biological root-like structures with periodontal ligament attachment within the jawbone and are capable of bearing occlusal loads. Nevertheless, the controllability of tissue dimensions and root morphology still requires further optimization.

3.3. Whole-tooth regeneration

The technical challenges associated with whole-tooth regeneration are substantially greater. A complete tooth comprises a complex three-dimensional architecture characterized by cusps, fossae, and ridges. Rather than being formed randomly, its morphology results from repeated induction and reciprocal interactions between the dental epithelium and the dental mesenchyme [9]. The core technical principle of whole-tooth regeneration is therefore to reconstruct the reciprocal inductive signaling axis between the dental epithelium and the dental mesenchyme, relying on the "dialogue" between these two cell populations to accomplish the morphogenesis of the tooth germ. Mouse studies have demonstrated the successful transplantation of bioengineered teeth with functional periodontal ligaments and sensory function. Subsequently, large-animal studies have further validated the feasibility of bioengineered tooth germ formation, eruption, and functional integration [7]. Nevertheless, the cell source and morphological control remain limiting factors for clinical translation. From the laboratory-level goal of "growing a tooth" to the clinical-level goal of "growing a tooth with both desirable morphology and function", numerous scientific questions remain to be answered. Morphological control currently represents a prominent challenge: although dental tissues such as dentin and enamel can frequently be generated in animal models, the faithful reproduction of fine anatomical features such as cusps and pits and fissures remains unsatisfactory, making it difficult to replicate the complex anatomical morphology of human teeth.

4. Clinical translation bottlenecks and comparison of restorative approaches

4.1. Major technical and translational bottlenecks

The factors hindering the clinical translation of regenerated teeth are multifaceted, among which the following three aspects are particularly prominent. The first is the issue of vascularization. Cells cultured in vitro can obtain nutrients from the culture medium, however, after implantation in vivo, in the absence of a pre-existing vascular network at the implantation site, the supply of oxygen and nutrients depends solely on passive diffusion. When the regenerated tissue exceeds the oxygen diffusion limit (approximately 100–200 μm), the cells in its interior are highly susceptible to necrosis [9]. Existing strategies, such as prevascularization and co-culture with endothelial cells, can partially ameliorate this problem, but they still fall short of meeting the blood supply demands of large-volume dental tissue [4]. The second is the challenge of precise morphological control. How to replicate the complex three-dimensional anatomy of human teeth has not yet been effectively resolved. Tooth development depends on spatiotemporally ordered signaling interactions between the

epithelium and the mesenchyme, and it is currently difficult to fully recapitulate this precisely regulated program in vitro. In animal experiments, dental tissue can often be generated, yet the development of fine anatomical features such as cusps and pits and fissures frequently exhibits malformations [9].

The third is the complexity of the oral immune microenvironment, which represents a significant translational barrier. The oral cavity is a microbe-laden environment with persistent microbial stimulation and harbors both innate and adaptive immune cells locally. After implantation, the cell–scaffold complex must, on the one hand, resist the inflammatory interference caused by bacteria and their toxins. The inflammatory microenvironment can suppress the odontogenic differentiation of stem cells and even induce their apoptosis, thereby impeding dental tissue regeneration. On the other hand, allogeneic cells can trigger host immune rejection responses, which may destroy the newly formed regenerated tissue [4]. Animal experiments are mostly conducted under relatively controlled surgical conditions with a low risk of infection, whereas the inflammatory burden and microbial load in the real clinical oral environment are far higher than those in animal experimental settings, consequently, the favorable outcomes obtained in vitro and in animal experiments can be readily attenuated in humans. Furthermore, the quality control, long-term safety, and regulatory standards of cell products have not yet been unified. Stem cell-based products carry potential risks of immune reactions, aberrant differentiation, and even tumorigenesis, and the complete procedures for cell preparation, expansion, and cryopreservation lack unified industry standards. This has also greatly delayed the transition from animal experiments to human clinical application [4].

4.2. The coexistence pathway of regenerated teeth and conventional restorative approaches

A more rational assessment is that regenerated teeth will not, and may not need to, replace mature restorative modalities such as dental implants or fixed bridges in the foreseeable future. A more realistic developmental scenario may follow the following progressive pathway: ccompared with conventional dental implants, the key advantages of regenerated teeth lie in their potential to restore the periodontal ligament and proprioception, with biomechanics more closely resembling those of natural teeth, their disadvantages, however, include the immaturity of the technology, high treatment costs, and limited cell availability. The two are not substitutes for each other, but rather complementary, serving different clinical needs.

In the near term, regenerative endodontic therapy is expected to first establish its clinical foothold in the treatment of immature permanent teeth with pulp necrosis [11]. In the mid-term, the combination of biological tooth roots with implant superstructures may evolve into a "semi-regenerative, semi-prosthetic" hybrid restorative approach, aimed at reducing the occurrence of peri-implant bone resorption [10]. In the long term, should whole-tooth regeneration achieve a breakthrough, it may provide edentulous patients with a biological alternative closely resembling natural teeth. Nevertheless, the timeline for its clinical application still depends on whether key issues—including cell sources, morphological control, safety, and standardized production—can be resolved [4].

5. Conclusion

In summary, the field of regenerated teeth has advanced from early conceptual proposals to a stage in which substantial effects can be observed in animal models. Various technical routes—including pulp regeneration, biological tooth root construction, and even whole-tooth regeneration—have all achieved a certain degree of feasibility validation within their respective experimental systems. At present, regenerative endodontic therapy has established a foundation for clinical application, whereas biological tooth roots and whole-tooth

regeneration remain primarily at the animal and preclinical stages. However, if mature clinical products are taken as the benchmark, it is fair to state that a considerable distance still remains before this goal is reached.

The limitations of this review are mainly reflected in the following aspects. First, the majority of currently available research literature derives from animal experiments, with relatively limited reports having truly entered the stage of human clinical trials. Second, there is substantial heterogeneity among studies in terms of experimental conditions, cell sources, scaffold materials, and evaluation criteria, which renders direct cross-study comparisons difficult. Consequently, with regard to the clinical translation timeline and long-term efficacy of regenerated teeth, all current judgments should be regarded as reasonable extrapolations based on available evidence rather than definitive conclusions.

Looking ahead, the deeper value of regenerated tooth technology may lie not only in providing a novel therapeutic option, but also in advancing the transformation of restorative dentistry from a philosophy of "artificial material replacement" toward "biological reconstruction". Naturally, this transformation will not be achieved overnight, its realization depends on the sustained collaboration and deep integration of multiple disciplines, including developmental biology, materials engineering, and clinical dentistry.

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